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AN EXPEDIENT ROUTE TO 1H-BENZIMIDAZOLES AND 1H-IMIDAZOPYRIDINES

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ABSTRACT

1H-Benzimidazoles, 1H-imidazo[4,5-b]pyridines, and 1H-imidazo[4,5-c]-pyridines can be synthesized readily by reaction of unisolated N-(1-chloro-alkyl)pyridinium chlorides with 1,2-benzenediamines, 2,3-pyridinediamine, and 3,4-pyridinediamine respectively.

INTRODUCTION

2-Substituted 1H-benzimidazoles[1, 2] are well kwown in the fields of pharmaceuticals, anthelmintics, and fungicides. They are generally prepared by heating a 1,2-benzenediamine with a carboxylic acid in hydrochloric acid. However this procedure affords 2-aryl derivatives in poor yields.

An alternative route consists in the reaction of the diamine with an aldehyde and further oxidation of the so-obtained imine. This variant is widely applicable but it requires two steps and isolation of the desired products is sometimes tedious.

As N-(1-haloalkyl)azinium halides[3-6] are advantageous precursors for the preparation of nitrogen heterocycles, [7-9] it was tempting to study their chemical behavior towards 1,2-benzenediamines.

RESULTS

In a typical experiment, 1,2-benzenediamine (three equivalents) was added to a solution of N-(chlorophenylmethyl)pyridinium chloride (2a, prepared *in situ*) in dichloromethane at room temperature. After a classical work-up procedure, we could rule out the formation of an imine or a dihydro-benzimidazole because of the absence, in the ^{1}H NMR spectra, of a signal around 8.5 ppm (HC=N) or 5.0 ppm (C^2-H) respectively. In addition, the molecular weight (mass spectrometry) of the product was m/z = 194. This corresponds to a loss of two hydrogen atoms from such structures.

This forced us to conclude that the reaction product was 2-phenyl-1H-benzimidazole (**4a**; 95 % yield calculated on the starting aldehyde). This was confirmed by comparison with spectral and physical data of a commercially available pure sample of **4a**.

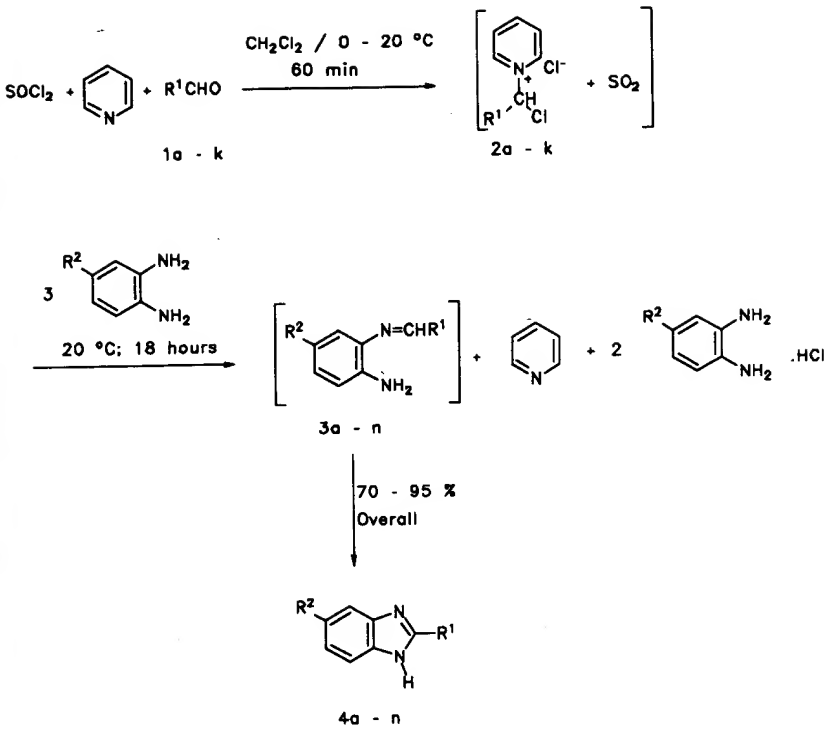
Direct formation of **4a** is not unique as thirteen other 1H-benzimidazoles (see Table 1) have been prepared in the same way. Overall yields (based on the aldehydes) are good to excellent as they exceed 70 % without having been optimized.

Table 1. Selected Data for 1H-Benzimidazoles **4**.

	Overall Yield (%)[a]	^{1}H NMR[b] δ R	Lit. Ref.
a	95	8.1-8.3 (m, 2H)[c]	12, 13
b	75	0.9 (t, 3H), 1.8 (m, 2H), 2.8 (t, 2H)	14
c	75	1.3 (d, 6H), 3.1 (m, 1H)	15
d	70	1.4 (s, 9H)	16
e	80	5.7 (s, 1H), 7.5 (s, 10H)	17
f	80	2.4 (s, 3H), 8.2 (d, 2H)[c]	18
g	70	8.3 (s, 4H)	13, 19
h	75	7.9-9.1 (c, 4H)	20, 21
i	75	8.3 (d, 2H)[c]	22
j	80	6.7 (dd, 1H), 7.9 (d, 1H)[c]	23
k	75	7.3 (c, 1H), 7.9 (dd, 1H), 8.2 (dd, 1H)	24
l	75	2.3 (s, 3H), 8.1 (d, 2H)[c]	22
m	70	8.4 (s, 4H)	24
n	70	8.2 (d, 2H)[c]	25

[a]: based on the aldehyde. [b]: DMSO-d_6/TMS; δ N-H: between 5.0 and 9.5; δ H^4-H^7 : 7.2-7.8 (c) ppm. [c]: other signals are overlapped.

The determining role played by sulfur dioxide (evolved during the formation of the salts) was again[9] ascertained as follows: N-[chloro(3-nitrophenyl)methyl]pyridinium chloride (**2h**) was isolated (by filtration) and reacted under our conditions (dichloromethane at room temperature) with 1,2-benzenediamine to afford N-[(3-nitrophenyl)methylene]-1,2-benzenediamine (**3h**) (80 % yield). On the other hand, when this imine **3h** was suspended in the solution in which salt **2h** had been prepared, it cyclized to 2-(3-nitrophenyl)-1H-benzimidazole (**4h**) within a few hours (75 % yield). The latter result suggests that our one-pot synthesis of the benzimidazoles **4** could proceed through the transient formation of imines. Further steps of the reactions would involve a ring-chain tautomerism with dihydrobenzimidazoles followed by the dehydrogenation.



1, 2	R^1	3, 4	R^1	R^2
a	Ph	a	Ph	H
b	n-Pr	b	n-Pr	H
c	iPr	c	iPr	H
d	t-Bu	d	t-Bu	H
e	$(Ph)_2CH$	e	$(Ph)_2CH$	H
f	$4\text{-}MeC_6H_4$	f	$4\text{-}MeC_6H_4$	H
g	$4\text{-}(NO_2)C_6H_4$	g	$4\text{-}(NO_2)C_6H_4$	H
h	$3\text{-}(NO_2)C_6H_4$	h	$3\text{-}(NO_2)C_6H_4$	H
i	$4\text{-}ClC_6H_4$	i	$4\text{-}ClC_6H_4$	Cl
j	2-Furanyl	j	2-Furanyl	H
k	2-Thienyl	k	2-Thienyl	H
		l	$4\text{-}MeC_6H_4$	Cl
		m	$4\text{-}(NO_2)C_6H_4$	NO_2
		n	$4\text{-}ClC_6H_4$	NO_2

Scheme 1

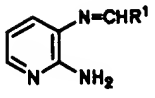
We also observed that yields decrease dramatically when the whole procedure is performed under a flow of dry nitrogen. Since oxidation by atmospheric oxygen seems unlikely (most imines derived from 1,2-benzenediamines are not air-sensitive), we rationalize our results as follows: sulfur dioxide is known[10] to form highly hygroscopic addition complexes with amines; therefore, appreciable amounts of hydrogen sulfite are present in the solvent and this oxidizing species[11] can be responsible for the formation of 1H-benzimidazoles (or 1H-perimidines[9]) but, obviously, only when the intermediate N-(1-haloalkyl)azinium halides are not isolated and when the syntheses are carried out under atmospheric conditions.

We extended our work by studying the chemical behavior of (unisolated) N-(1-chloroalkyl)pyridinium chlorides towards pyridinediamines. Indeed preparation of 1H-imidazopyridines, which are known to be potent cardiotonic agents,[26] often requires drastic conditions like prolonged heating in polyphosphoric acid.[27, 28]

Thus, we found that treatment of 4-methylbenzaldehyde with a mixture of thionyl chloride and pyridine in dichloromethane, followed by reaction with 2,3-pyridinediamine (three equivalents) produced 3-[(4-methylphenyl)-methylene]amino-2-pyridineamine (5). We reasoned that experimental conditions were too mild to effect the conversion of the imine into the imidazopyridine system. This led us to mix the reactants in chlorobenzene, to check the formation of the imine 5, and then to heat the reaction mixture under reflux for 4 hours. In this way, the final product we isolated was 2-(4-methylphenyl)-1H-imidazo[4,5-b]pyridine 6 (85 % yield). Compounds 7 - 12 (Table 2) were prepared similarly.

From a mechanistic point of view, these results confirm that imines are obligatory intermediates in the reactions described in this work. Therefore, N-(1-haloalkyl)azinium halides effectively behave like the precursor aldehydes towards N-nucleophiles. The aromatization step is only due to the evolution of sulfur dioxide during their preparation. The solubility of the intermediate imines and their propensy to cyclise are among the factors that govern the rate of that aromatization step. The necessity of heating the reaction mixtures to obtain imidazopyridines under our conditions is probably due to a combination of both factors: imine 5, for example, is poorly soluble in common organic solvents and the amino group in position 2 of the pyridine ring is weakly nucleophilic.[29, 30]

TABLE 2. Selected Data for Compounds 5 - 12.



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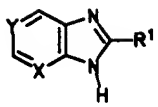

6 - 12

	X	Y	R^1	Overall Yield (%)[a]	^1H NMR[b] (ppm)	Lit. Ref.
5			4-MeC_6H_4	85	2.4 (s, 3H, CH_3), 6.1 (br, 2H, NH_2), 6.7 (dd, 1H, H^5), 7.3 (c, 3H, H^3 and H^5 Ar, H^4), 8.1 (c, 3H, H^2, and H^6 Ar, H^2), 8.7 (s, 1H, N=CH)	31
6	N	CH	4-MeC_6H_4	85	2.4 (s, 3H, CH_3), 6.0 (br, 1H, NH), 7.3 (dd, 1H, H^5), 7.4 (d, 2H, H^3 and H^5 Ar), 8.1 (dd, 1H, H^6), 8.2 (d, 2H, H^2 and H^6 Ar), 8.4 (dd, 1H, H^4)	27
7	N	CH	Ph	80	6.8 (br, 1H, NH), 7.3 (dd, 1H, H^5), 7.8 (c, 3H, H^3, H^4, and H^5 Ar), 8.1 (dd, 1H, H^6) 8.3 (c, 2H, H^2 and H^6 Ar), 8.4 (dd, 1H, H^4)	27
8	N	CH	3-(NO_2)C_6H_4	80	[c]	28
9	N	CH	2-ClC_6H_4	90	5.8 (br, 1H, NH), 7.3 (dd, 1H, H^5), 7.6-7.8 (c, 3H, H^3, H^4, and H^5 Ar), 8.0 (c, 1H, H^6 Ar), 8.1 (dd, 1H, H^6), 8.4 (dd, 1H, H^4)	28
10	N	CH	2-Thienyl	85	6.9 (br, 1H, NH), 7.3 (dd, 1H, H^5), 7.4 (dd, 1H, H^4 Th), 7.8-8.0 (c, 2H, H^3 and H^5 Th), 8.1 (dd, 1H, H^6), 8.4 (dd, 1H, H^4)	27
11	CH	N	4-MeC_6H_4	75	2.4 (s, 3H, CH_3), 6.4 (br, 1H, NH), 7.4 (d, 2H, H^3 and H^5 Ar), 7.6 (d, 1H, H^7), 8.2 (d, 2H, H^2 and H^6 Ar), 8.4 (d, 1H, H^6), 9.0 (s, 1H, H^4)	26
12	CH	N	4-FC_6H_4	70	5.6 (br, 1H, NH), 7.4 (t, 2H, H^3 and H^5 Ar), 7.7 (d, 1H, H^7), 8.3 (d, 1H, H^6), 8.4 (d, 2H, H^2 and H^6 Ar), 9.1 (s, 1H, H^4)	26

[a]: based on the aldehyde. [b]: DMSO-d_6/TMS. [c]: insoluble.

In conclusion, we have found a new one-pot method for preparing 1H-benzimidazoles, 1H-imidazo[4,5-b]pyridines, and 1H-imidazo[4,5-c]pyridines. It could not be foreseen and it is characterized by its simplicity. By comparison with classical routes, it requires milder conditions, it appears to be more general and it can give higher yields. For example, 5-chloro-2-(4-chlorophenyl)-1H-benzimidazole (4i) was prepared in 36 % yield from 4-chloro-1,2-benzenediamine and the bisulfite adduct of 4-chlorobenzaldehyde.[32] Through our procedure, we could obtain 4i in 75 % yield. Another noteworthy improvement is illustrated by the synthesis of 1H-imidazopyridines since, through our method, the use of hot polyphosporic acid [27, 28] is unnecessary. In addition, excess of diamines and pyridine can be recovered and recycled, if necessary.

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EXPERIMENTAL

All compounds were characterized by their spectral data (^{1}H NMR: Varian EM 360-L; IR: Perkin-Elmer 577; MS: Varian Mat 311A). Melting points (uncorrected) were determined on a hot-stage microscope. Compounds 1a-k[3-8] and 3h[24] have been described in the literature. For the other derivatives, the corresponding references are quoted in the Tables.

General procedure for the preparation of 1H-benzimidazoles

A solution of thionyl chloride (0.9 ml; 12 mmol) in dichloromethane (10 ml) was cooled down to 0 °C. Then a solution of pyridine (1.0 ml; 12 mmol) in dichloromethane (6 ml) was added dropwise followed by the aldehyde (10 mmol). The mixture was allowed to warm to room temperature for one hour and formation of the N-(1-chloroalkyl)pyridinium chloride was confirmed by NMR.[4] The diamine (30 mmol) was then slowly added and stirring was maintained overnight. The solvent was evaporated under reduced pressure and the residue was triturated with water to yield the crude final product.

General procedure for the preparation of 1H-imidazopyridines

A solution of thionyl chloride (0.9 ml; 12 mmol) in chlorobenzene (10 ml) was cooled down to 0 °C. Then pyridine (1.0 ml; 12 mmol) was added dropwise followed by the aldehyde (10 mmol). The mixture was allowed to warm to room temperature for one hour during which time the pyridinium salt separated from the solvent. The diamine (30 mmol) was then slowly added and stirring under reflux was maintained for 4 hours. The solvent was evaporated under reduced pressure and the residue was triturated with a solution of sodium hydroxide (0.1 M; 3 X 10 ml). The crude imidazopyridine was filtered and thoroughly washed with water.

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